REMARKS

The present paper is being filed in response to a **non-final** office action dated November 7, 2008, which set a three-month shortened statutory period for response. The instant response is timely filed on March 9, 2009, by virtue of the fact that March 7, 2009, was a Saturday, and by virtue of the attached petition and fee for a one-month extension of time.

A. Status of the Claims

Claims 4, 14, 18 and 24-28 are pending in the instant case. The claims stand variously rejected under 35 U.S.C 112, first paragraph for allegedly lacking written description and 35 U.S.C. 103(a) as assertedly being obvious in view of a combination of references. Applicants respectfully traverse the rejection and request reconsideration thereof in view of the following remarks.

B. Rejection under 35 U.S.C. 112, first paragraph should be withdrawn

Claims 24-28 stand rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement Applicants respectfully traverse the rejection and provide the following comments for the Examiner's consideration.

Claim 24 was objected to because in step (b) discusses to separate products of step (a) to obtain 3(tert-butyldimethylsiloxy)-5-hydroxybenzaldehyde and in step (d) it discloses purification of the oil produced in step (c). Also there is an objection that step (c) refers to sieves are rinsed in solvent whereas the specification teaches ethyl acetate. Step (f) was objected to because it recites deprotection and them separation of product

of step (e) whereas according to the examiner the specification only discloses separation by gravity column chromatography.

The examiner admits that the specification teaches the use of a flash chromatography method to separate and therefore to purify 3(tert-butyldimethylsilyloxy)-5 hydroxybenzaldehyde. The skilled person understands that "flash" chromatography refers to a separation technique based on column chromatography in which air pressure is used to speed the flow rate of the solvent. This teaching of "flash" chromatography in the specification to purify 3(tert-butyldimethylsilyloxy)-5 hydroxybenzaldehyde would teach the skilled person that the preparation prior to the chromatography contained a mixture and the chromatography step is the purification step. The manner in which this intermediate is purified is not essential to the method and the ordinary skilled person could accomplish separation and consequently purification of 3(tert-butyldimethylsilyloxy)-5 hydroxybenzaldehyde using any number of separation techniques routine in chemical arts. The key step is the separation of the 3(tert-butyldimethylsilyloxy)-5 hydroxybenzaldehyde from the other products of step (a) and not specifically the manner in which it is separated. In *Dow Chem. Co. v, Sumitomo Chem. Co. Ltd.* 257 F3d 1364 (Fed Cir. 2001) the Court noted that the language of the claims defines the scope of the invention and as a starting point claim terms are given their ordinary and accustomed meaning. Given the teaching in the specification that chromatography is used to purify the products, the skilled person would understand that step b to "separate" the products is taught by the specification.

For the same reasons as presented above, the Examiner's objection to steps 24 (e) and (f) and claim 25 step (g), 28(j) should also be withdrawn. The specification

teaches gravity column chromatography as a separation method. This is an ordinary and exemplary separation technique and the skilled person would be well aware that it can readily be substituted by another readily available separation technique.

The Examiner objected to step (c) stating that the specification only provides support for ethyl acetate for the rinsing step and not the use of a "solvent". Ethyl acetate is a solvent. The skilled person would understand it to be such. It is simply used in the specification as a carrier solvent to facilitate recovery of the reaction product. Upon reading the specification those of ordinary skill will readily understand that it is being used to wash and recover to produce a yield of the product. The specification teaches that the solution 3(tert-butyldimethylsilyloxy)-5 hydroxybenzaldehyde dichloromethane, molecular sieves and trimethyloxonium tetrafluoroborate had been stirred for 15 hours after which the solution was filter and the sieves rinsed with ethyl acetate and the solvent removed from the combined filtrate. The claim has been amended to state that the sieves are rinsed with ethyl acetate.

Claims 25, 27 and 28 were objected to because the examiner feels the specification only teaches protecting by adding Hunig's base. The skilled person knows that there are various techniques to protect a particular moiety during chemical synthesis. However, Applicants have amended step (a) in each of these claims. This overcomes the rejection.

Claim 26 step (a) was objected to because according to the Examiner there is no disclosure therein of a step of reacting 4-methoxybenzyltriphenylphosphonium bromide and 3,5 di-(tert-butyldimethylsilyloxy)-benzaldehyde. Applicants respectfully refer the

Examiner to page 8, line 4 of the specification which expressly teaches that 4-methoxybenzyltriphenylphosphonium bromide (i.e., Compound 3) is a starting material for stilbene synthesis. In the specification at page 16, lines 3-15 there is a specific teaching of preparation of stilbenes by reaction of compound 3 with a compound 9(a). Compound (9a) specifically is 3,5 di-(tert-butyldimethylsilyloxy)-benzaldehyde. Given this disclosure in the specification, there is an express teaching of reacting methoxybenzyltriphenylphosphonium bromide with 3,5 di-(tert-butyldimethylsilyloxy)-benzaldehyde in the specification and this step is expressly depicted at page 37 of the original application as filed and written in descriptive format at page 16, lines 3-15.

Applicants believe the above response overcomes all the objections under 35 U.S.C. 112 first paragraph. Applicants therefore request that the rejections be withdrawn.

C. Rejection under 35 U.S.C. 103(a) should be withdrawn

The Examiner set forth 2 separate rejections of the claims for allegedly being obvious. Applicants respectfully traverse both rejections and provide the following response to the rejection.

i. Rejection of claims 4, 14 and 18

Claims 4, 14 and 18 were rejected under 35 U.S.C. 103(a) as being unpatentable over Ghai et al. (US 2002/0028852) in view of Seyedi et al. (US 6,743,937) and further in view of Orsini et al (Carbohydrate Research Vo. 301, Issue 3-4, June 1997, pp 95-109). Briefly summarizing and highlighting the Examiner's reasoning, it is the

Examiner's assertion that Ghai et al discloses ***an analog*** of resveratrol (3,5,4' trihydroxystilbene) and a method of treating cancer in an animal using such a composition. The examiner goes on to state that Ghai et al differ from the instant claims ***in that the reservatrol analog does not contain the phosphate group.*** Having made this determination, the Examiner adds to the rejection Seyedi which the Examiner states teaches combretastatin A-4, ***which is similar in structure and function as the resveratrol analogs disclosed by Ghai***, and that Seyedi teaches to ***phosphorylate the compound combrestatin A-4***. Orisini is cited for disclosing synthesis of polyphenolic glycosides.

According to the Examiner it "would have been obvious to phosphorylate the resveratrol analogs of Ghai as taught by Seyedi et al. with a reasonable expectation of success, since the compounds are similar in structure and have been shown by Orsini et al to undergo similar synthesis." Applicants respectfully submit that the present invention has nothing to do with phosphorylation of the compounds taught in Ghai.

A close reading of the claims 4, 14 and 18 of the present invention shows that the compounds of the present invention differ from those of the art taught by Ghai not just because they are phosphorylated, but because they are a different class of compound: the resverastatin compounds of the present invention are **3,5-dimethoxy**-4-hydroxy-stilbene. The teaching of Ghai highlighted by the Examiner on the other hand is of a compound that is a **3,5-4'-trihydroxy**-stilbene. Hence there is a fundamental molecular structural difference between the novel compounds of the present invention and the trihydroxy-stilbene taught by Ghai.

In order to establish a *prima facie* case of obviousness, the combined disclosure references as a first step must provide a complete teaching of the claimed elements. Nothing in the combined disclosure of Ghai, Seyedi and Orsini provides a teaching of all of the elements of the claims compound. The combined art does not teach that the hydroxy groups that are present at each of positions 3 and 5 of **3,5-4'-trihydroxy**-stilbene taught by Ghai should be replaced by –OCH3 (methoxy groups) or could be replaced and **yet still produce an active compound**. In the absence of such teachings, there seems to be little point in proceeding to a discussion of yet another class of compounds: the combretastatin A-4 compound of Seyedi and phosphorylation thereof. Indeed as explained in the current specification, it was an objective of the present invention to provide **alternative active derivatives** of combretastatin A-4.

Moreover, the specific compound of the present invention, **3,5-dimethoxy**-4-hydroxy-stilbene (resverastatin) much like resveratrol, is essentially inactive against the assembly of tubulin as noted in the application (See Tables I-II). In addition, resverastatin also functions as a very useful antifungal and antibacterial substance and that data is also included in the specification (See Tables I-II). Combretastatin A-1 and A-4 do not possess these properties.

None of the stilbenes taught in the combination of references corresponds to the resverastatin claimed in the present invention and there is no teaching in the art that suggests that modification of the stilbenes in the prior art to specifically methylate the 3,5-dihydroxy groups of resveratrol would have produced a substance with biological properties that so closely mimic those of resveratrol.

Indeed, the obviousness analysis in the present case should proceed according to the guidance provided by the Federal Circuit in *Eisai v. Dr. Reddy* 533 F3d 1353; 87 U.S.P.Q. 2D 1452 (Fed. Cir. 2008; attached). In that case the Federal Circuit specifically addressed the obviousness of chemical compounds post-KSR. In that case the claims related to rabeprazole and its salts. The only difference between the claimed compound and the compound of the prior are was that the prior art compound "at the 4-position on the pyridine ring ... has a trifluoroethoxy (OCH_2CF_3) substituent, whereas rabeprazole has a methoxypropoxy ($OCH_2CH_2CH_2OCH_3$) substituent."

The Federal Circuit specifically stated that "in cases involving new chemical compounds, ***it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner*** to establish prima facie obviousness of a new claimed compound." Moreover, the Court teaches us that "to the extent an art ***is unpredictable, as the chemical arts often are***, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions" are not likely to be predictable. Thus, according to the Federal Circuit, obviousness of chemical cases post KSR cannot rely just on finding of an appropriate lead compound in the prior art.[1]

Much like the case in Eisai v. Dr. Reddy, while 3,5,4 tihydroxystilbene compounds may well have been known in the art and their modification to

[1] In holding that teachings of lansoprazole do not render obvious a claim to rabeprazole, the Court stated "post-KSR, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound. Teva cannot create a genuine issue of material fact on obviousness through the unsupported assertion that compounds other than lansoprazole might have served as lead compounds. Further, the record contains no reasons a skilled artisan would have considered modification of lansoprazole by removing the lipophilicity-conferring fluorinated substituent as an identifiable, predictable solution. In sum, the district court properly concluded that the record did not support a case of obviousness of the '552 patent as a matter of law."

phosphorylated groups may well have been suggested, that alone is not sufficient to support prima facie obviousness of a claim to a **3,5-dimethoxy**-4-hydroxy-stilbene (resverastatin) that may be phosphorylated. The examiner must show the the art teaches the desirability of changing just the 3,5 hydroxy groups to methoxy groups and couple that teaching with a suggestion that making those changes will still produce an active compound. The Examiner simply has not shown why the skilled artisan would have modified a **3,5-4'-trihydroxy**-stilbene into a **3,5-dimethoxy**-4-hydroxy or that it would be expected to have good activity.

In regard to the activity of the compounds issue, **3,5-dimethoxy**-4-hydroxy stilbene compound of the present invention and its phosphate prodrug represent new compositions of matter that would not have been predicted to have good properties as anticancer agents but not significantly inhibit tubulin. Even in its phosphorylated prodrug form, the **3,5-dimethoxy**-4-hydroxy stilbene strongly inhibits growth of the MCF-7 breast cancer cell line (see Tables I and III of the application) and has strong cancer cell growth inhibitory activity among the related benzhydrols and benzophenone new compositions of matter summarized in Table II.

Furthermore, Applicants respectfully submit that as a practical matter, the Examiner's statement that "the skilled artisan would have been motivated to phosphorylate the resveratrol analog of Ghai *et al.* as taught by Seyedi *et al.* in order to improve its water solubility is misleading. **3,5-dimethoxy**-4-hydroxy stilbene is not taught in the prior art. To arrive at the present invention, the skilled person would not only have to modify the prior art hydroxy compounds they would also have to phosphorylate them and the Examiner has provided no reasoning why a chemist

instead of following the ordinary course of preparing an alkali metal salt of the one 3,5-4'-trihydroxy-stilbene would instead both modify the hydroxyl groups of the prior art stilbenes to methoxy groups and then on top of that synthesize a phosphate derivative thereof and then convert the phosphate derivative to an alkali metal phosphate salt and still expect the end compound to be active.

Moreover, if the skilled person were to proceed as suggested by the examiner to attempt to simply phosphorylate the trihydroxy stilbene of Ghai, *at al.*, the result would have be an extended series of synthetic challenges to prepare a monophosphate of that triphenol or completely phosphorylate to a triphosphate. Both approaches would have been fraught with technical problems and there is no teaching in the cited art as to how to overcome those problems.

In view of the above discussion, Applicants respectfully submit that claims 4, 14 and 18 are non-obvious and respectfully request the Examiner to reconsider and withdraw the rejection.

ii. Rejection of claims 24-28 should be withdrawn

According to the Examiner Orsini et al. disclose synthesis of biologically active polyphenolic gycosides (combretastatin and resveratrol) and that the "compounds are synthesized almost identical to the instant resveratrol derivatives" because "the use of molecular sieve and proton sponge would have been an obvious matter of operator preference and that a change in the sequence of adding ingredients is considered to be prima facie obvious. Applicants respectfully disagree.

At the outset, it is important to understand that relying on case law by way of illustration that "disclosing a process of making a laminated sheet wherein a base sheet is first coded with a metallic film and thereafter impregnated with a thermo setting material" where it was considered "obvious" that reversing the process would make no difference might be true in certain cases in metallurgy but is completely wrong for designing successful organic syntheses of a specific chemical compound.

As organic research chemists well know, there can be a tremendous difference in the order of adding reactants/solvents in eliminating hazards to personnel along with achieving a successful reaction outcome. For example, if one was carrying out a hydrogenation reaction, by first filling the reaction flask containing solvent and reactant with hydrogen gas and then adding, for example, the finely divided platinum metal catalyst, the result could predictably be explosion/fire! In general, the effect of reagent additions in terns of order is more subtle and comes from a vast knowledge of experience with similar reactions. That knowledge and experience makes the difference between an unsuccessful or successful outcome and potential invention.

Moving to the specific synthesis method being claimed for the synthesis of a **,5-dimethoxy**-4-hydroxy stilbene phosphate and related substances as disclosed, the reaction conditions are very important in terms of reagent addition sequences and isolation procedures: Here, it is also important to note that in the Orsini et al *Carbohydrate Research* paper cited by the Examiner, the authors were primarily making synthetic modifications of combretastatin A-1 and A-4 and that chemistry was based on earlier syntheses of both substances already available in the literature.

By contrast, the synthetic techniques benefited from further research in this area presented in the present specification to provide novel and specific combination of steps to produce 5-dimethoxy-4-hydroxy stilbene phosphate derivative. Again, the Orsini citation is focused only on glycoside prodrugs, not phosphates. In the absence of a teaching in the art of the specific steps for the process for the production of 5-dimethoxy-4-hydroxy stilbene phosphate the method cannot be rendered obvious by a teaching of methods of producing glycoside prodrugs.

The Commissioner is authorized to charge any additional fees or credit any overpayment to the Deposit Account of McAndrews, Held & Malloy, Account No. 13-0017.

Dated: March 9, 2009

Respectfully submitted,

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abandoned the only defense available to it.[7] Thus we are presented with no argument on appeal that suggests that the district court erred in following our mandate.

AFFIRMED.

EISAI CO. LTD. and Eisai, Inc., Plaintiffs–Appellees,

v.

DR. REDDY'S LABORATORIES, LTD. and Dr. Reddy's Laboratories, Inc., Defendants–Appellants,

and

Teva Pharmaceuticals USA, Inc., Defendant–Appellant.

Nos. 2007–1397, 2007–1398.

United States Court of Appeals, Federal Circuit.

July 21, 2008.

Rehearing and Rehearing En Banc Denied Sept. 16, 2008.

Background: Patentee of patent claiming lead compound used in pharmaceutical approved for the treatment of duodenal ulcers, heartburn, and associated disorders brought infringement action against competitors. The United States District Court for the Southern District of New York, Gerard E. Lynch, J., 472 F.Supp.2d 493, 2006 WL 2872615, granted in part and denied in part owner's motions for summary judgment, and found competitors infringed patent. Competitors appealed.

Holdings: The Court of Appeals, Rader, Circuit Judge, held that:

(1) prior art did not render patent obvious, and

(2) patentee did not commit inequitable conduct in prosecuting patent application for patent.

Affirmed.

1. Patents ⇐16.13

Obviousness, for patent law purposes, is ultimately a legal question, based on underlying factual determinations. 35 U.S.C.A. § 103(a).

2. Patents ⇐16(2, 3), 36.1(1)

The factual determinations underpinning the legal conclusion of obviousness,

Appellant's Br. at 18, n.8 (emphasis added).

Second, effectively arguing a defense under Art. V(1)(c), Consorcio argues that the district court did "not comply with this court's mandate to balance the Convention's policy favoring confirmation of arbitral awards against the principle of international comity embraced by the Convention." Appellants' Br. at 19 (quoting *Four Seasons*, 377 F.3d at 1171). Our admonition to balance policies favoring arbitration and international comity was directed to the court's discretion, however, "even if the court finds that Article V(1)(a) applies." *Four Seasons*, 377 at 1171. As explained *supra*, in Part I of this opinion, Article V of the New York Convention gives a court discretion to refuse enforcement only after a defense has been shown. Because the court did not find that Consorcio had shown a defense under Article V(1)(a), it did not err by not considering Consorcio's international comity arguments.

7. There is no question that determining which substantive law governs the validity of the arbitration agreement is a logical precursor to determining whether the agreement is valid. Because Consorcio has waived its defense that the agreement is invalid, however, we need not address the district court's conclusion that the agreement is subject to United States law.

for patent law purposes, include: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, also known as objective indicia of non-obviousness. 35 U.S.C.A. § 103(a).

3. Patents ⇐324.5

In reviewing a district court's summary judgment of non-obviousness in a patent infringement proceeding, the appellate court reviews the record for genuine issues of material fact without deference, bearing in mind the movant's burden to prove invalidity by clear and convincing evidence. 35 U.S.C.A. § 103(a).

4. Patents ⇐16.25

Where the patent at issue claims a chemical compound, the analysis of the third *Graham* factor for determining obviousness, the differences between the claimed invention and the prior art, often turns on the structural similarities and differences between the claimed compound and the prior art compounds; obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound in a particular way to achieve the claimed compound. 35 U.S.C.A. § 103(a).

5. Patents ⇐16.25

The requisite motivation to prove the obviousness of a patent claiming a chemical compound based on structural similarity can come from any number of sources and need not necessarily be explicit in the art; rather it is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old. 35 U.S.C.A. § 103(a).

6. Patents ⇐16.25

Prior art did not render obvious patent claiming lead compound used in pharmaceutical approved for the treatment of duodenal ulcers, heartburn, and associated disorders, where compounds claimed by prior art differed structurally from compound claimed by patent, and the record contained no reasons a skilled artisan would have considered the differences between the compounds identifiable and predictable. 35 U.S.C.A. § 103(a).

7. Patents ⇐324.54, 324.55(2)

Where a judgment regarding inequitable conduct in prosecuting a patent application follows a bench trial, the appellate court reviews the district court's findings of materiality and intent for clear error and its ultimate conclusion for an abuse of discretion.

8. Patents ⇐97

Inequitable conduct in prosecuting a patent application before the Patent and Trademark Office (PTO) may take the form of an affirmative misrepresentation of material fact, a failure to disclose material information, or the submission of false material information, but in every case this false or misleading material communication or failure to communicate must be coupled with an intent to deceive; "materiality," defined as "what a reasonable examiner would have considered important in deciding whether to allow a patent application," and intent are both questions of fact, and require proof by clear and convincing evidence.

See publication Words and Phrases for other judicial constructions and definitions.

9. Patents ⇐97

To satisfy the "intent" prong for unenforceability of a patent due to inequitable conduct during the prosecution of a patent application, the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive; gross negligence is not sufficient.

10. Patents ⇐97

Patentee did not commit inequitable conduct in prosecuting patent application for patent claiming lead compound used in pharmaceutical approved for the treatment of duodenal ulcers, heartburn, and associated disorders by failing to disclose its own co-pending application, withholding rejections from its co-pending application that also would have applied to patent, failing to disclose prior art, submitting a misleading declaration, and concealing similar compound, where record lacked sufficient evidence of intent to deceive.

Patents ⇐328(2)

4,255,431. Cited as Prior Art.

Patents ⇐328(2)

5,045,552. Infringed.

Joseph M. O'Malley, Jr., Paul, Hastings, Janofsky & Walker, LLP, of New York, New York, argued for plaintiffs-appellees. With him on the brief were Bruce M. Wexler, David M. Conca, Gary G. Ji, and Quinn E. Clancy.

Maurice N. Ross, Budd Larner, P.C., of Short Hills, New Jersey, argued for defendants-appellants Dr. Reddy's Laboratories, Ltd., and Dr. Reddy's Laboratories, Inc. With him on the brief were Andrew J. Miller, Louis H. Weinstein, Ellen T. Lowenthal, and Dmitry V. Sheluho.

Henry C. Dinger, Goodwin Procter LLP, of Boston, Massachusetts, argued for defendant-appellant Teva Pharmaceuticals USA, Inc. With him on the brief were Elaine H. Blais, and David M. Hashmall, Frederick H. Rein, and Emily L. Rapalino, of New York, New York.

Before RADER, LINN, and PROST, Circuit Judges.

RADER, Circuit Judge.

On summary judgment, the United States District Court for the Southern District of New York found in favor of plaintiffs Eisai Co., Ltd. and Eisai, Inc. (collectively Eisai) with respect to the validity and enforceability of U.S. Patent No. 5,045,552 ('552 patent). *Eisai Co. v. Teva Pharms. USA, Inc.*, 472 F.Supp.2d 493 (S.D.N.Y.2006) (*SJ Validity Order*); *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, No. 03 Civ. 9053 (S.D.N.Y. Oct. 5, 2006) (*SJ Enforceability Order*). After a bench trial, the district court found that Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (collectively Dr. Reddy's) and Teva Pharmaceuticals USA, Inc. (Teva) had failed to prove the remaining allegations of inequitable conduct, and that Eisai had established that Dr. Reddy's and Teva infringed Eisai's '552 patent. *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, No. 03 Civ. 9053, 2007 WL 1406565 (S.D.N.Y. May 11, 2007) (*Trial Order*). Because the district court correctly determined that the '552 patent is non-obvious over the proffered prior art and that Eisai's alleged acts during prosecution did not rise to the level of inequitable conduct, this court affirms.

I

The '552 patent claims rabeprazole and its salts. Rabeprazole is part of a class of drugs known as proton pump inhibitors, which suppress gastric acid production by inhibiting action of the enzyme H^+K^+ATPase. The distinctions between rabeprazole and its salts are not relevant for this appeal. Therefore this court refers to rabeprazole and its salts collectively as "rabeprazole." Rabeprazole's sodium salt is the active ingredient in Aciphex, a pharmaceutical approved in 1991 by the FDA for the treatment of duodenal ulcers, heartburn, and associated disorders. Aciphex has been a commercial success, garnering over $1 billion in worldwide yearly sales.

Dr. Reddy's and Teva each filed Abbreviated New Drug Applications (ANDAs) under the Hatch–Waxman Act, 21 U.S.C. § 355 and 35 U.S.C. § 271(e), seeking to manufacture a generic version of Aciphex before the expiration of the '552 patent. Because filing an ANDA is an artificial, but legally cognizable, act of patent infringement, *see Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1344 (2004), Eisai filed suit against Dr. Reddy's and Teva. Eisai also sued Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc. (collectively Mylan), another ANDA filer, but that proceeding was stayed pending the outcome of these actions. Mylan agreed to be bound by the final judgments and any appeals in these cases. *Eisai Co., Ltd. v. Mylan Labs., Inc.*, No. 04 Civ. 656 (S.D.N.Y. Nov. 3, 2004). Both Dr. Reddy's and Teva conceded infringement of claims 1–6 of the '552 patent, but asserted that the '552 patent is unenforceable for inequitable conduct. *Trial Order* at 6–7. Dr. Reddy's stipulated to the validity of all six of the '552 patent's claims, *id.* at 6, but Teva argued before the district court and maintains on appeal that the '552 patent is invalid for obviousness. Both Dr. Reddy's and Teva appeal the trial court's judgments of enforceability. Neither Dr. Reddy's nor Teva appeals the trial court's judgment of infringement. This court has jurisdiction under 28 U.S.C. § 1295(a)(1).

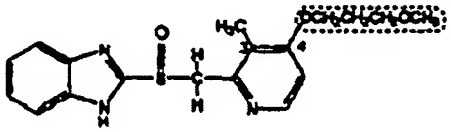
II

[1–3] This court reviews a grant of summary judgment without deference. *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1362 (Fed.Cir.2003). Obviousness under 35 U.S.C. § 103(a) is ultimately a legal question, based on underlying factual determinations. *See Richardson–Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed.Cir.1997). The factual determinations underpinning the legal conclusion of obviousness include 1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). Thus, in reviewing a district court's summary judgment of non-obviousness, this court reviews the record for genuine issues of material fact without deference, bearing in mind the movant's burden to prove invalidity by clear and convincing evidence. *See Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed.Cir.1998).

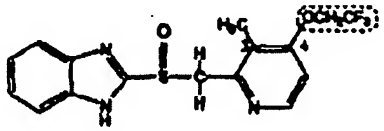
[4, 5] Where, as here, the patent at issue claims a chemical compound, the analysis of the third *Graham* factor (the differences between the claimed invention and the prior art) often turns on the structural similarities and differences between the claimed compound and the prior art

compounds. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377 (Fed.Cir.2006) (noting that, for a chemical compound, a prima facie case of obviousness requires "structural similarity between claimed and prior art subject matter ... where the prior art gives reason or motivation to make the claimed compositions" (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed.Cir.1990) (en banc))). Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound. *See Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed.Cir.2007). In keeping with the flexible nature of the obviousness inquiry, *KSR Int'l Co. v. Teleflex Inc.*, —— U.S. ——, 127 S.Ct. 1727, 1739, 167 L.Ed.2d 705 (2007), the requisite motivation can come from any number of sources and need not necessarily be explicit in the art. *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed.Cir.2007). Rather "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship ... to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Id.* (quoting *Dillon*, 919 F.2d at 692).

[6] Teva asserts that a combination of three prior art references renders the '552 patent obvious: 1) European Patent No. 174,726 (owned by Takeda), claiming lansoprazole (EP '726); 2) United States Patent No. 4,255,431 (to Junggren), claiming omeprazole ('431 patent); and 3) an article by Brändström, et al., entitled "Structure Activity Relationships of Substituted Benzimidazoles" (Brändström). EP '726 teaches, inter alia, the ulcer treatment compound lansoprazole. Lansoprazole differs structurally from rabeprazole at the 4–position on the pyridine ring, as indicated in the diagram below. Lansoprazole has a trifluoroethoxy (OCH_2CF_3) substituent, whereas rabeprazole has a methoxypropoxy ($OCH_2CH_2CH_2OCH_3$) substituent.



Rabeprazole

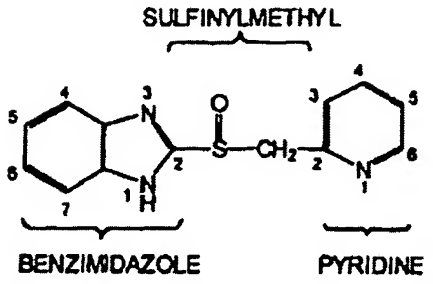


Lansoprazole

Appellant Teva's Br. at 28. Otherwise, the two compounds are identical. *See SJ Validity Order* at 7. Both rabeprazole and lansoprazole are "asymmetrically substituted" with respect to the 4–position on the pyridine ring because the substituent at the 3–position (a methyl group in both compounds) is not the same as the substituent at the 5–position (a hydrogen in both compounds).

The '431 patent discloses a broad class of gastric acid inhibiting compounds, including omeprazole, the first commercial proton pump inhibitor, sold as Prilosec. Although sharing the same basic structure, omeprazole is structurally farther afield from rabeprazole than is lansoprazole. For instance, omeprazole's pyridine ring is symmetrically substituted and has a methoxy (OCH3) group at the 4–position.

Finally, Brändström describes a class of anti-ulcerative compounds having a benzimidazole-sulfinylmethyl-pyridine core (the Brändström core structure):



Brändström Core Structure

Rabeprazole, lansoprazole, and omeprazole are all Brändström core structure compounds. Taking the evidence in the light most favorable to Teva, this court assumes that as per EP '726, lansoprazole is twenty times superior to omeprazole for anti-ulcer action, as measured by an indomethacin-induced gastric lesion assay in rats. This court also assumes that lansoprazole has certain traits, including lipophilicity (the ability of a compound to cross lipid membranes) and low molecular weight, that would have made it desirable to a skilled artisan.

Under these assumptions, one of skill in this art may have considered it a candidate for a lead compound in the search for anti-ulcer compounds. To the contrary, the district court emphasized the differences between anti-ulcer action and gastric acid inhibition. The trial court specifically noted that Teva's expert testified with respect to the EP '726 data that "[t]he level of acid secretion ... from these [anti-ulcer] data ... cannot be determined." *SJ Validity Order* at 13. In this context, this court consults the counsel of *KSR* that "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." 127 S.Ct. at 1742. Thus lansoprazole's candidacy as a starting point to develop new anti-ulcer compounds versus new gastric acid inhibitors does not resolve the lead compound analysis, at least not in the absence of any contrary indications. *Cf. Takeda*, 492 F.3d at 1359 (negative side effects could dissuade one of skill from using a particular compound as a starting point).

Nonetheless, as the district court noted, the EP '726 reference teaches at best that the fluorinated substituent of lansoprazole provides "a *special path* to achieving lipophilicity." *SJ Validity Order* at 10 (emphasis in original). And Teva's expert identified a separate reference teaching that fluorine-substituted groups increase lipophilicity. *Id.* The record, however, shows no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property. Indeed, Teva's pharmacology expert, Dr. John Forte, declined to opine on lansoprazole's relevance to an examiner assessing the patentability of rabeprazole. J.A. at 14894. And Dr. Reddy's pharmacology expert, Dr. Simmy Bank, testified in deposition that "I thought [lansoprazole] had nothing to do with this trial." J.A. at 14756.

This court notes that the district court did not rigidly limit Teva's obviousness arguments by forcing Teva to select a single lead compound. Rather Teva alone

selected lansoprazole as the anchor for its obviousness theory, not the district court. In *KSR*, the Supreme Court noted that an invention may have been obvious "[w]hen there [was] ... a design need or market pressure to solve a problem and there [were] ... a finite number of identified, predictable solutions." 127 S.Ct. at 1742 (tense changes supplied to clarify, as the Court stated and as per 35 U.S.C. § 103, that the obviousness inquiry must rely on evidence available "at the time" of the invention, *see Takeda*, 492 F.3d at 1356 n. 2). The Supreme Court's analysis in *KSR* thus relies on several assumptions about the prior art landscape. First, *KSR* assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, *KSR* presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. *See Takeda*, 492 F.3d at 1357 ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."). Third, the Supreme Court's analysis in *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S.Ct. at 1742. In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed.Cir.2008), this court further explained that this "easily traversed, small and finite number of alternatives ... might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

In other words, post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound. Teva cannot create a genuine issue of material fact on obviousness through the unsupported assertion that compounds other than lansoprazole might have served as lead compounds. Further, the record contains no reasons a skilled artisan would have considered modification of lansoprazole by removing the lipophilicity-conferring fluorinated substituent as an identifiable, predictable solution. In sum, the district court properly concluded that the record did not support a case of obviousness of the '552 patent as a matter of law.

III

[7] As with other summary judgment issues, this court reviews a district court's summary judgment on inequitable conduct without deference. *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1378 (Fed.Cir. 2008). In contrast, where a judgment regarding inequitable conduct follows a bench trial, this court reviews the district court's findings of materiality and intent for clear error and its ultimate conclusion for an abuse of discretion. *ACCO Brands, Inc. v. ABA Locks Mfrs. Co.*, 501 F.3d 1307, 1314 (Fed.Cir.2007).

[8, 9] Inequitable conduct in prosecuting a patent application before the United States Patent & Trademark Office may take the form of an affirmative misrepresentation of material fact, a failure to disclose material information, or the submis-

sion of false material information, but in every case this false or misleading material communication or failure to communicate must be coupled with an intent to deceive. *Innogenetics*, 512 F.3d at 1378 (citations omitted). Materiality, defined as "what a reasonable examiner would have considered important in deciding whether to allow a patent application," and intent are both questions of fact, and require proof by clear and convincing evidence. *Id.* To satisfy the "intent" prong for unenforceability, "the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 876 (Fed.Cir.1988) (en banc) (citing *Norton v. Curtiss*, 57 C.C.P.A. 1384, 433 F.2d 779 (1970)). Gross negligence is not sufficient. *Id.* This is a high bar.

[10] On appeal, Teva and Dr. Reddy's allege that Eisai misled the Patent Office in five ways: 1) failing to disclose Eisai's own co-pending '013 application, which claimed the "ethyl homolog" of rabeprazole (compound SHKA 661); 2) withholding rejections from the '013 application's prosecution that also would have been applicable to the '552 patent's prosecution; 3) failing to disclose the prior art "Byk Gulden patent" (WO 8602646); 4) submitting a misleading declaration (the Fujisaki Declaration) to the examiner of the '552 patent; and 5) concealing lansoprazole from the examiner. The district court rejected the fifth assertion on summary judgment, *SJ Enforceability Order* at 58, and the other four after a bench trial, *Trial Order*.

Teva and Dr. Reddy's first and second allegations rely on Eisai's failure to disclose the fact of, and rejections contained in, Eisai's patent application claiming the "ethyl homolog" of rabeprazole. Known to Eisai's scientists as compound SHKA 661, the ethyl homolog differs from rabeprazole as its name suggests. SHKA 661 has one fewer methylene unit at the 4–position of the pyridine ring, giving SHKA 661 an ethoxy group rather than a propoxy group at this position. The district court correctly pointed out that calling SHKA 661 the "ethyl homolog" of rabeprazole in this case could carry a misleading implication with respect to inequitable conduct. The record supplies no evidence to suggest that Eisai's scientists ever referred to SHKA 661 by this name, or thought of SHKA 661 and rabeprazole "primarily in relation to each other." *Trial Order* at 17 n. 7. Rather, the district court found credible the testimony that Eisai scientists considered SHKA 661 separately patentable, even though Eisai ultimately did not pursue that course. *Id.* at 22–23; 42–43. Furthermore, even if a provisional obviousness-type double-patenting rejection might have issued in the prosecution of the '552 patent due to the co-pending SHKA 661 application, the district court found the materiality of this potential situation low, because applicants routinely overcome this type of rejection, *id.* at 44, by amending claims or filing a terminal disclaimer. Nonetheless, the district court did not hold that the fact of the copendency of these two applications to be totally immaterial, accurately noting that applicants should be encouraged to disclose closely related applications. *Id.* at 47.

While disclosure of the co-pending SHKA 661 application to the Patent Office during the prosecution of the '552 patent would have been prudent, Eisai's failure to do so is by no means fatal, for two reasons. First, the district court had ample evidence from which to conclude that the materiality of the SHKA 611 application

was low, as outlined above. Second, the record is devoid of any real suggestion of intent to deceive the Patent Office, much less the clear and convincing evidence required to support a finding of inequitable conduct.

As for the rejections of the '013 application that would have been relevant to the prosecution of the '552 patent, the district court did not reach materiality because it discerned insufficient proof of intent to deceive. The district court found the documentary evidence (faxed exchange between Eisai employees Mr. Shuhei Miyazawa, one of the inventors of the '552 patent, and Mr. Mitsuo Taniguchi, Eisai's patent agent, regarding Mr. Miyazawa's presentation to a pharmaceutical trade industry group) to supply no compelling evidence of intent, based on testimony from both parties to the fax. Witness credibility determinations lie squarely within the district court's discretion. *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1171 (Fed.Cir. 2006). The district court was ultimately undisturbed by the Taniguchi/Miyazawa communication based on its evaluation of the witness testimony presented, and this court sees no abuse of discretion. These facts certainly do not rise to the level of "culpability" this court required in *Kingsdown*, 863 F.2d at 876, to establish intent to deceive, or even gross negligence.

Finally, the district court found that Teva's theory that Eisai deliberately hid the ball from the Patent Office by separately filing the '552 and '013 prosecutions to be "implausibly risky," given that such similar applications would usually be assigned to the same examiner in the same art unit. *Trial Order* at 53. The district court thus had ample bases from which to conclude that Eisai's failure to disclose its co-pending '013 application along with the rejections issued in its prosecution, while not completely forthcoming, did not rise to the level of inequitable conduct.

With respect to the Byk Gulden patent, Teva and Dr. Reddy's argue that Eisai's failure to disclose this reference to the Patent Office during prosecution of the '552 patent was material because a reasonable examiner would have used it to issue a new and stronger prima facie obviousness rejection on the basis of Byk Gulden's disclosure of asymmetrically-substituted compounds having a methoxyethoxy at the 4-position of the pyridine ring. But the district court found Byk Gulden's teachings cumulative with references already disclosed to the Patent Office (Junggren or Junggren combined with Beecham). As per 37 C.F.R. § 1.56, cumulative evidence is definitionally not material evidence. *See Monsanto Co. v. Bayer Bioscience N.V.*, 514 F.3d 1229, 1237 (Fed.Cir.2008). Here, the Junggren reference specifically disclosed asymmetrically substituted compounds, including a compound having a 4-position methoxyethoxy substituent. Thus the Byk Gulden reference offered nothing new to the record already before the Patent Office. And even Teva's expert conceded Byk Gulden would not have provided the examiner with anything new. *Id.* at 57. Thus the district court was well within its discretion in concluding that the Byk Gulden patent was not material to the prosecution of the '552 patent. Even if Byk Gulden had been material, the lack of clear and convincing evidence of intent to deceive would nonetheless have imposed an insurmountable bar to finding inequitable conduct, for the reasons given by the district court.

As for the Fujisaki Declaration, Eisai submitted it during prosecution to overcome an obviousness rejection. Because this reference shows rabeprazole's pharmacological properties, the trial court found it highly material. *Id.* at 59. Teva

and Dr. Reddy's argue that the data presented in the Fujisaki Declaration were misleading. They contend that the comparison with two non-prior art compounds without a comparison of the ethyl homolog of rabeprazole, SHKA 661, sent the examiner on a dead-end side trip. The district court properly characterized this argument as "contorted." *Id.* The Fujisaki Declaration indisputably showed a comparison between rabeprazole and the prior art compound called out by the examiner, demonstrating rabeprazole's superiority. Further, as discussed above, the materiality of SHKA 661 and the patent application claiming it was low. The data from the Fujisaki Declaration were relevant to prosecution, but Eisai had no obligation to include additional, unnecessary data such as a comparison to SHKA 661. Thus the district court did not abuse its discretion in concluding that Eisai did not commit inequitable conduct in failing to include additional data in the Fujisaki Declaration to the examiner. Even here, where the submission to the Patent Office itself was highly material to prosecution, the lack of deceptive intent rendered stillborn yet another allegation of inequitable conduct.

Finally, Teva and Dr. Reddy's assert that that Eisai deceptively declined to inform the examiner of a patent application for lansoprazole, a prior art proton pump inhibitor (and the active ingredient in Prevacid). The district court disposed of this argument on summary judgment. The district court found that Teva and Dr. Reddy's had presented neither direct evidence of deceptive intent nor any evidence to support an inference of materiality. *SJ Enforceability Order* at 58. The strongest evidence of some problem was the passing comment of one Eisai "insider" that the similarity of lansoprazole and rabeprazole "bothers me." *Id.* at 59. But this vague, subjective statement is not sufficient by any means to establish materiality, let alone intent. Moreover, given lansoprazole's fluorinated substituent and its resultant impotence to render the '552 patent invalid, the district court properly rejected this strained theory of inequitable conduct on summary judgment.

IV

In a series of thoughtful, thorough opinions, the district court carefully explained its reasoning with respect to both obviousness and inequitable conduct. Because the district court properly concluded that Teva and Dr. Reddy's failed to prove that the '552 patent was invalid for obviousness or unenforceable for inequitable conduct, this court affirms the district court's judgment.

AFFIRMED

COSTS

Each party shall bear its own costs.

BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM, Plaintiff–Appellant,

v.

BENQ AMERICA CORP., Motorola, Inc., Hon Hai Precision Industry Co. Ltd., and Chi Mei Communication Systems, Inc., Defendants–Appellees,

and

Kyocera Wireless Corp., Defendant–Appellee,

and

Innostream, Inc., Toshiba Corporation, and Wistron Corporation, Defendants,

and

HTC Corp., High Tech Computer Corporation, Sanyo North America Corp., LG Electronics Mobilecomm U.S.A., Inc., Sendo America, Inc., Sie-